Oxidative Stress and Cardiovascular Diseases

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Cardiovascular diseases (CVD) are complex entities with heterogenous pathophysiologic mechanisms and increased oxidative stress has been viewed as one of the potential common etiologies. A fine balance between the presence of reactive oxygen species (ROS) and antioxidants is essential for the proper normal functioning of the cell. A basal concentration of ROS is indispensable for the manifestation of cellular functions, whereas excessive levels of ROS cause damage to cellular macromolecules such as DNA, lipids and proteins, eventually leading to necrosis and apoptotic cell death. CVD is the main cause of death worldwide with several conditions being affected by oxidative stress. Increased ROS lead to decreased nitric oxide availability and vasoconstriction, promoting arterial hypertension. ROS also negatively influence myocardial calcium handling, causing arrhythmia, and augment cardiac remodeling by inducing hypertrophic signaling and apoptosis. Finally, ROS have also been shown to promote atherosclerotic plaque formation.

antioxidants oxidative stress nutraceuticals cardiovascular diseases

1. Introduction

A variety of cardiovascular diseases have been shown to be associated, at least partially, with an excess production of reactive oxygen species (ROS) [1][2][3][4]. ROS constitute both oxygen free radicals, such as superoxide, hydroxyl radicals, and peroxyl radicals, as well as non-radicals, such as hydrogen peroxide, hypochlorous acid, and ozone [5]. In most cell types, mitochondria are the main drivers of intracellular oxidant production, while other relevant sources are nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (summarized as the NOX family of enzymes). Apart from that, numerous other enzymes such as xanthine oxidase, nitric oxide synthase, cyclooxygenases, cytochrome P450 enzymes, and lipoxygenases as well as other cell organelles, like the peroxisome and endoplasmic reticulum, contribute to intracellular ROS production [6]. Proteins, lipids and DNA are the primary cellular structures affected by ROS and reactive nitrogen species (RNS). The generation of molecular oxygen in the form of ROS is a natural part of aerobic life. Indeed, basal levels of ROS are essential for the manifestation of various cellular functions, such as signal transduction pathways, defense against invading microorganisms, gene expression and the promotion of growth or death [7]. In spite of the crucial relevance of redox reactions, dysregulation of oxidant signaling may cause or accelerate a host of pathological conditions, such as the rate of aging. However, the body is equipped with protective measures against ROS via enzymatic (e.g., superoxide dismutase (SOD), catalase (CAT), peroxiredoxin (Prx) and glutathione peroxidase (GSH-Px)) as well as non-enzymatic compounds (e.g., tocopherol/vitamin E, beta-carotene, ascorbate, glutathione (GSH), and nicotinamide (NAM)) [8]. Newer research tools allow the investigation of redox signaling pathways in adequate chemical detail, and it has become clear that redox processes are as important in biology as

phosphorylation-dephosphorylation reactions, or central mechanisms responsible for controlling the genome and epigenome, such as acetylation–deacetylation and methylation–demethylation [9]. However, the analysis of redox systems is challenging due to the substantial subcellular differences in redox potential and the short lifespan of ROS. The discovery of numerous biomarkers of oxidative stress has facilitated the measurement of ROS; however, their clinical use still needs to be validated given the vast diversity in oxidative stress between different diseases. Genomics, epigenomics, and exposomics along with methodologies for redox imaging, redox proteomics, and redox metabolomics, will improve our understanding of health and disease processes within entire biological systems. Furthermore, the emerging big data and artificial intelligence era will provide us with new opportunities for the development of oxidative stress knowledge bases and paves the way for a more personalized redox medicine [9].

In 2016, ≈17.6 million deaths were attributed to cardiovascular diseases (CVD) globally, which amounted to an increase of 14.5% from 2006 [10]. CVD is currently the leading cause of death, and it claims more lives each year than cancer and chronic lung disease combined. Coronary heart disease (CHD) represents the most common CVD [10]. In the coming decades, with an aging population and increased incidence of obesity and diabetes, the burden and medical costs of CVD are anticipated to significantly increase worldwide. Although significant efforts have been made to enlighten pathophysiologic mechanisms governing the initiation and progression of CVD, still much work has to be done [11][12][13]. As such, a better understanding of the biomolecular mechanisms and their clinical consequences is urgently needed to reduce the burden of CVD, and this poses a serious challenge in medicine.

2. Endothelial Dysfunction in Cardiovascular Disease

The endothelium is a highly active monolayer that plays important roles in modulating vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation. This is achieved by the production and release of several endothelium-derived relaxing factors, including vasodilator prostaglandins, nitric oxide (NO), and endothelium-dependent hyperpolarization factors, as well as endothelium-derived contracting factors. These vasoactive molecules that relax or constrict the vessel play a direct role in the balance of tissue oxygen supply, long-term organ perfusion, remodeling of vascular structures, and metabolic demand by regulation of vessel tone and diameter [14][15]. Endothelial cells dispose of an enzyme to fight vascular disease, namely endothelial nitric oxide synthase (eNOS), which generates the vasoprotective molecule NO. This molecule diffuses to the vascular smooth muscle cells, activates soluble guanylyl cyclase and increases cyclic guanosine monophosphate (cGMP) [16]. NO can also inhibit leukocyte adhesion to the vessel wall which represents an early event in the development of atherosclerosis; therefore, NO may protect against the onset of atherogenesis. Furthermore, NO is also involved in the inhibition of platelet aggregation and adhesion, both of which protect smooth muscle cells from exposure to platelet-derived growth factors. These mechanisms can lead to fibrous plaque formation; therefore, NO also prevents a later step in atherogenesis. NO suppresses key processes in vascular lesion formation and thus probably represents the most important antiatherogenic defense principle in the vasculature [16].

The pathomechanisms of endothelial dysfunction involve a diminished production and/or availability of NO, and a disproportion between the endothelium-derived vasodilators and vasoconstrictors. Several traditional cardiovascular risk factors are associated with alteration in endothelial function such as smoking, sedentary and incorrect lifestyle, aging, hypercholesterolemia, arterial hypertension, hyperglycemia, and a family history of premature atherosclerotic disease (**Figure 1**) [17][18]. This leads to chronic inflammation, resulting in an increase in vasoconstrictor and prothrombotic products and diminished antithrombotic factors, in addition to abnormal vasoreactivity, all of which elevate the risk of cardiovascular events. Indeed, endothelial dysfunction has also been linked with obesity, elevated C-reactive protein, and chronic systemic infection [18]. Oxidative stress and inflammation are the main drivers of endothelial dysfunction. Several oxidative enzyme systems such as NADPH oxidase, xanthine oxidase, cyclooxygenases, lipoxygenases, myeloperoxidases, cytochrome P450 monooxygenase, uncoupled NOS, and peroxidases lead to the inactivation of NO, which represents a critical mechanism leading to endothelial dysfunction through an elevated level of superoxide anion ($O_2^{\bullet-}$) [19]. Both NADPH oxidase and eNOS uncoupling (i.e., the generation of ROS through eNOS as part of endothelial activation) act as important sources of $O_2^{\bullet-}$ that give rise to vascular oxidative stress. Inhibition of NADPH oxidase has been established as a key molecular mechanism leading to reduced arterial oxidative stress and normalization of endothelial dysfunction in mice [20]. Inflammation has been shown in many studies to play a role in endothelial dysfunction that underlies the pathogenesis of CVD, obesity and type 2 diabetes mellitus. Both in rodents and humans, elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1 β), interleukin-6 (IL-6), and interferon gamma (IFN-γ) have been observed in age-related endothelial dysfunction, mainly via the activation of the nuclear factor-kappa B (NF-κB) pathway [21][22][23][24][25][26]. NF-κB is an important transcription factor that regulates the gene expression of factors responsible for cell adhesion, proliferation, inflammation, redox status, and tissue specific enzymes. It is expressed in all cell types and plays a major role in the promotion of CVD through the transcription of pro-inflammatory, pro-adhesion and pro-oxidant genes [27]. The NF-κB pathway can be activated by a variety of stimuli including inflammatory cytokines, ROS, lipids and mechanical forces acting on the vascular endothelial wall. Upon activation, transmembrane receptors are stimulated which trigger intracellular signaling pathways, culminating in the activation of a kinase (IκK) mediated phosphorylation and degradation of the inhibitor of NF-κB (IκB). Subsequently, the NF-κB heterodimer (p65/p50 subunits and, perhaps, p65, RelB, c-Rel, p50 and p52) translocates to the nucleus, where it binds to promoters of gene targets. Several other pro-inflammatory molecules have been associated with endothelial dysfunction, such as IL-6, TNF-α, monocyte chemoattractant protein 1 (MCP-1), receptor for advance glycation endproducts (RAGE) and the pro-oxidant enzyme NADPH oxidase, and all predispose the vasculature to a “proatherogenic” phenotype [28][29][30].

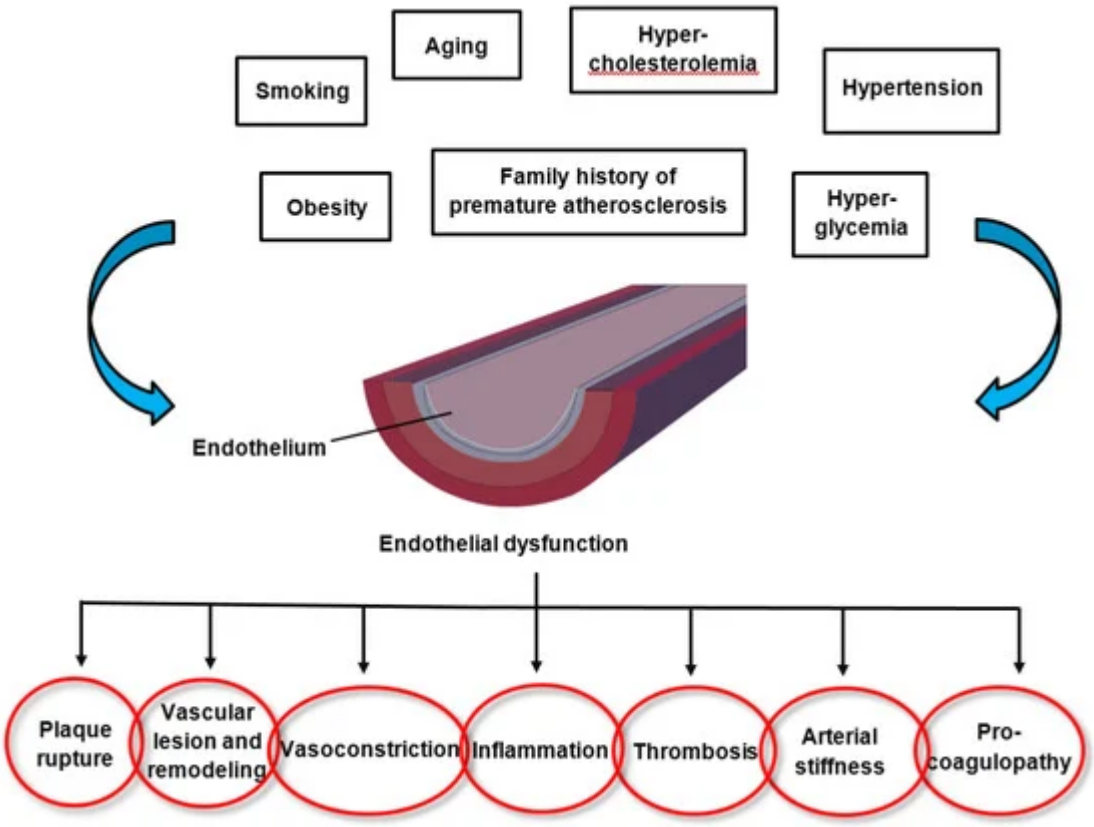

Figure 1. Factors altering endothelial function and the consequences of endothelial dysfunction.

The endothelium has an endogenous capacity for repair, which occurs via two mechanisms. Lost and damaged cells can be replaced by locally replicating mature endothelial cells. However, this repair mechanism is insufficient in the presence of risk factors and loss of endothelial integrity would rapidly ensue. Circulating endothelial progenitor cells represent an alternative mechanism for maintenance and repair of the endothelium; they are recruited from the bone marrow. These cells circulate in the peripheral blood and have the ability to differentiate into mature cells with endothelial characteristics [15]. Indeed, factors that have been shown to have a positive impact on endothelial function, such as exercise and statins, have also been shown to have a potent positive effect on the mobilization of endothelial progenitor cells [31][32]. The importance of the balance between exposure to risk factors and the efficiency of endothelial repair has been underscored by the observation that subjects with increased numbers of circulating endothelial progenitor cells have preserved endothelial function, despite exposure to high levels of risk factors [33].

Endothelial therapy can be viewed as a two-step approach. The best treatment for diseases is preventing the disease from occurring in the first place. Therefore, the first approach is disease prevention through increased awareness and control of cardiovascular risk factors by nonpharmacological measures such as lifestyle optimization (e.g., a healthy diet, physical exercise, maintaining a normal body weight). The second approach is targeted (pharmacological) therapy directed at preserving or restoring the function of already impaired endothelial cells in order to defer disease progression, promote disease stabilization, improve overall quality of life, reduce disability and health costs, and ultimately increase survival [34]. The aim of pharmacological treatment is

reestablishing endothelial cell homeostasis (e.g., statin therapy to reduce low-density lipoprotein (LDL) cholesterol levels; antidiabetics to reduce blood glucose levels; antihypertensives to normalize blood pressure; heart failure therapy to amend myocardial and vasomotor function). Certain drugs may have some additional, endothelium-protective off-target effects, such as statins by reducing inflammation and some angiotensin antagonists also having metabolic (antidiabetic) effects [35][36]. Researchers are currently exploring new pathogenetic targets to improve vascular dysfunction, including anti-inflammatory agents, therapies based on microRNAs and epigenetic mechanisms. MicroRNAs (miRNAs) have been demonstrated to play a pivotal role during atherosclerotic plaque formation. Indeed, it has been established that both miR-143 and miR-181a are upregulated in human atherosclerotic plaques [37][38]. Hydrogen peroxide (H_2O_2) treatment induces an increase in miR-181a levels, while inhibition of miR-181a leads to increased resistance to H_2O_2, thus implying that miR-181a is involved in the oxidative stress-induced endothelial cell dysfunction [37]. MiR-133a may represent an additional target for preventing cardiovascular disease. Studies have demonstrated that the inhibition of aberrant miR-133a by lovastatin prevents endothelial dysfunction by targeting GTP cyclohydrolase 1, a critical enzyme for eNOS uncoupling in endothelial dysfunction [39]. Finally, inhibition of miR-92a, an important regulator of endothelial proliferation and angiogenesis after ischemia, leads to reduced endothelial inflammation, decreased plaque size, and a more stable lesion phenotype [40]. In recent years, emerging evidence has arisen that epigenetic pathways might also play an important role in endothelial dysfunction. Resveratrol, a member of the polyphenol group, is produced by several plants in response to injury and protects against pathological processes through the suppression of elevated levels of proinflammatory cytokines in macrophages. Increased TNF-α-induced CD40 expression has been shown to modify the expression levels of specific adhesion molecules, thus boosting the inflammatory response. Resveratrol treatment was able to attenuate the enhanced CD40 expression triggered by TNF-α stimulation. Furthermore, resveratrol suppressed TNF-α-triggered ROS via potentiating the activity of sirtuin 1 (a histone deacetylase involved in suppressing inflammation), thus protecting cells from damage generated by inflammatory factors [41].

3. Oxidative Stress and Inflammation in Cardiovascular Diseases

The NOX (for **N**ADPH **OX**idase) family NADPH oxidases are transmembrane proteins that transfer a single electron from NADPH onto molecular oxygen, leading to the formation of superoxide. The physiological generation of ROS usually occurs as a byproduct; however, this is not the case with NOX enzymes, as the generation of ROS represents their primary biological function. In fact, the NOX-mediated release of ROS, also known as oxidative burst, promotes the eradication of invading microorganisms in macrophages and neutrophils. The importance of ROS in the host immune response is accentuated by the fact that people with an inherited deficiency in NOX2 develop chronic granulomatous disease (CGD) and are incapable of warding off common infections. The first NADPH oxidase, NOX2, was found in phagocytes. This was followed by the discovery of other members of the NOX family NADPH oxidases, which are not limited to phagocytes, but can de facto be found in virtually every tissue [42]. There is substantial evidence indicating that NOX enzymes play an essential role in the pathophysiology of several CVD [43][44].

Inflammation is an adaptive reaction to harmful stimuli and certain conditions, such as infection or tissue injury, and comprises the regulated delivery of blood components (plasma and leukocytes) to the site of infection or injury. A contained inflammatory response is generally thought to be beneficial (e.g., granting protection against infection), but can become destructive if dysregulated (e.g., causing septic shock) [45]. We will subsequently discuss the roles of oxidative stress and inflammation in the most prevalent CVD. The underlying oxidative and inflammatory molecular mechanisms governing these CVD are summarized in **Figure 2**.

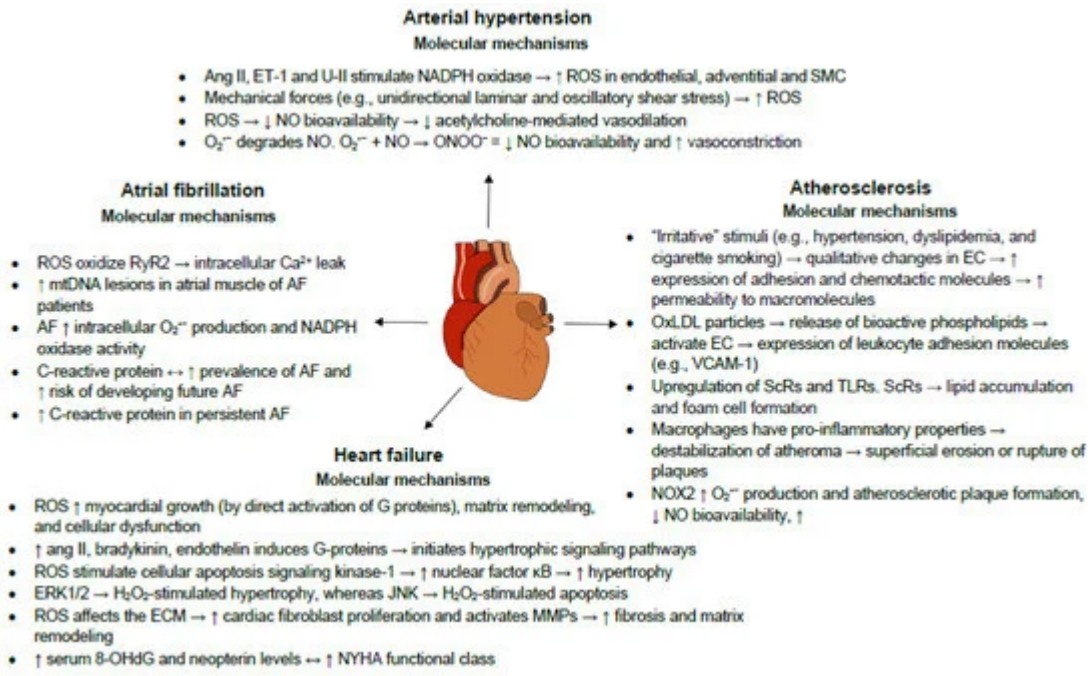

Figure 2. Selected cardiovascular diseases and their underlying oxidative and inflammatory molecular mechanisms. 8-OHdG: 8-hydroxy-2′-deoxyguanosine AF: atrial fibrillation; Ang II: angiotensin II; EC: endothelial cells; ECM: extracellular matrix; ERK 1/2: extracellular signal-regulated kinase 1/2; ET-1: endothelin 1; H_2O_2: hydrogen peroxide; JNK: c-Jun N-terminal kinase; MMP: matrix metalloproteinase; mtDNA: mitochondrial DNA; NADPH: nicotinamide adenine dinucleotide phosphate; NO: nitric oxide; NYHA: New York Heart Association; $O_2^{\cdot-}$: superoxide anion; $ONOO^-$: peroxynitrite; OxLDL: oxidatively modified LDL; ROS: reactive oxygen species; RyR2: type 2 ryanodine receptor; ScRs: scavenger receptors; SMC: smooth muscle cells; TLRs: toll-like receptors; U-II: urotensin II; VCAM-1: vascular cell adhesion molecule-1; →: leads to; ↔: associated with. Please refer to the text for more details.

4. Effects of Diet and Nutraceuticals on Oxidative Stress in Cardiovascular Diseases

Based on the prevalence of CVD and the role of ROS in many pathologies, as specified above for the cardiovascular system, there has long been interest in the application of naturally occurring antioxidants and the development of chemical antioxidative agents to ease or prevent CVD. The subsequent chapter outlines available

evidence regarding the effect of diet and nutraceuticals, i.e., the beneficial effects that substances contained in foods have on human health [46], on the prevention and therapy of oxidative stress in distinct CVD (**Table 1**).

Table 1. Diets and nutraceuticals investigated regarding their potential therapeutic antioxidant effects.

Study Reference	Diet/Nutraceutical(s)	Studied Population	Main Therapeutic Antioxidant Effects
[47]	Extra virgin olive oil	Human and in vitro studies	Stable platelet ROS generation, platelet and serum sNOX2-dp release, 8-iso-PGF2α-III formation, sVCAM1 and E-selectin levels and a NS ↓ in Vit E levels In vitro ↓ cell ROS and 8-iso-PGF2-III formation and NOX2 regulation
[48]	Dark chocolate (cocoa)	Human study	↓ platelet ROS and NOX2 activation, ↓ platelet production of 8-iso-PGF2a, ↑ platelet NOx levels after dark chocolate consumption in smokers
[49][50][51] [52][53][54] [55][56][57] [58]	Nuts	In vitro, animal and human studies	↓ lipid peroxidation, ↓ LDL oxidation, ↓ formation of TBARS, ↓ ROS-induced DNA strand scissions ↑ increase serum paraoxonase-1 and arylesterase activities ↓ DNA strand breaks in lymphocytes and 8-hydroxydeoxyguanosine urine concentrations
[59][60][61] [62][63][64] [65][66][67]	Tea polyphenols	In vitro, animal and human studies	Scavenging of superoxide and other ROS, inhibition of lipid peroxidation ↑ plasma antioxidant capacity ↓ blood pressure, heart failure and atherosclerosis risk
[68][69][70] [71]	Flavonoids	Animal and human studies	↑ acetylcholine-induced nitric oxide production, ↓ acetylcholinesterase activity ↑ eNOS expression and GSH/GSSG ratio ↑ flow-mediated dilation, ↓ blood pressure ↓ NOx, iNOS expression and $O_2^{\bullet-}$ production ↓ lipid peroxidation and protein oxidation

Study Reference	Diet/Nutraceutical(s)	Studied Population	Main Therapeutic Antioxidant Effects
[72][73][74]	The Mediterranean diet	Human studies	↑ adherence to the MD associated with ↓ oxidative stress and inflammation and ↑ endothelial function and insulin sensitivity ↑ diet score associated with ↑ GSH/GSSG ratio
[75][76][77][78][79][80]	PUFAs	In vitro, animal and human studies	↑ endothelial progenitor cells, ↓ endothelial microparticles inhibition of TLR and TNF-α pro-inflammatory signaling pathways, ↑ insulin sensitivity ↓ ROS-induced DNA damage, ↓ double-strand breaks, ↓ activation of kinases that initiate DNA damage response

8-OHdG: 8-hydroxy-2′-deoxyguanosine; 8-iso-PGF2α-III: 8-iso-prostaglandin F2α; eNOS: endothelial nitric oxide synthase; GSH: glutathione; GSSG: glutathione disulfide; iNOS: inducible nitric oxide synthase; LDL: low-density lipoprotein; MD: Mediterranean diet; NOx: the nitric oxide metabolites nitrite and nitrate; NOX2: NADPH oxidase 2; NS: not significant; PUFAs: polyunsaturated fatty acids; ROS: reactive oxygen species; sVCAM1: vascular cell adhesion molecule 1; sNOX2-dp: soluble NOX isoform 2; TBARS: thiobarbituric acid reactive substances; TLR: toll-like receptor; TNF: tumor necrosis factor; Vit.: vitamin.

5. Benefits and Harms of Antioxidants

Although some diets and nutraceuticals have shown antioxidant properties and even a reduction in cardiovascular morbidity and mortality, several trials investigating various antioxidants have shown no benefit or even harm. A meta-analysis examining the effect of antioxidant supplementation on mortality and health in 66 randomized trials found a positive outcome in 24, a null outcome in 39, and a negative outcome in 3 trials [81]. However, they found that the positive outcome studies included mostly individuals at risk of malnutrition. The outcome of studies examining antioxidant supplements will substantially depend on the nature of the cohort, including the age of the participants, their health status, economic status, toxicity of drug treatments etc. The authors found a benefit of antioxidant supplements mainly in those populations who are at risk of having nutrient deficiencies. Vitamins C and E, selenium, beta-carotene, and other nutrients such as zinc contribute to the antioxidant defense system. Therefore, individuals with inadequate intake of these vitamins and nutrients may benefit most from antioxidant supplementation. In contrast, individuals with an adequate nutrient status may have reached a threshold, and further antioxidant supplementation is unlikely to confer additional benefit. This threshold varies between each individual and is contingent on an individual's specific requirements with age, sex, health status, and nutrigenomic factors such as polymorphisms likely altering these requirements [81].

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has been suggested that the indiscriminate use of antioxidants may even be harmful [82] as discussed in the introduction. Free radical production occurs continuously in all cells as part of aerobic life and indeed, basal levels of ROS are imperative for certain cellular functions [7]. Decreasing the amount of free radicals in our organism may impede some essential defense mechanisms such as apoptosis, phagocytosis, and detoxification [83][84]. A fine balance between the magnitude of oxidative stress and antioxidants in our cells is of paramount importance for normal function in the cells and interfering with this balance may lead to untoward effects. The amount of antioxidants that may lend protection varies among individuals and likely depends upon their current oxidative status, as people subjected to increased oxidative stress or those with innate or acquired high baseline levels of ROS may have elevated antioxidant requirements. Conversely, for people with low innate levels of ROS, antioxidant supplementation may even be harmful [83][84]. Additionally, it has been proposed that endogenous antioxidant defenses may be far more important to humans than antioxidants gained from supplements or diet. Therefore, agents that increase endogenous antioxidant defenses and other protective systems may bring about a better protective effect on tissue damage caused by oxidative stress [83][84], rather than consumption of large amounts of vitamins [85].

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